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Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study

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SUMMARY

Objective: To clarify the association between the occurrence and progression of knee osteoarthritis (KOA) with components of metabolic syndrome (MS), including overweight (OW), hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT), in a general population.

Design: From the large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) initiated in 2005, 1,690 participants (596 men, 1,094 women) residing in mountainous and coastal areas were enrolled. Of these, 1,384 individuals (81.9%; 466 men, 918 women) completed the second survey, including knee radiography, 3 years later. KOA was defined as Kellgren–Lawrence (KL) grade ≥ 2 using paired X-ray films. Based on changes in KL grades between the baseline and second surveys, cumulative incidence and progression of KOA were determined. OW, HT, DL, and IGT at baseline were assessed using standard criteria.

Results: The cumulative incidence of KOA among 1,384 completers over 3 years was 3.3%/year, and progression in KL grades for either knee, 8.0%/year. Logistic regression analyses after adjusting for potential risk factors revealed that the odds ratio (OR) for the occurrence of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 2.33; two components, 2.82; $\geq$three components, 9.83). Similarly, progression of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 1.38; two components, 2.29; $\geq$three components: 2.80).

Conclusion: Accumulation of MS components is significantly related to both occurrence and progression of KOA. MS prevention may be useful in reducing future KOA risk.

Introduction

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly and affects activities of daily living and quality of life, leading to increased morbidity and mortality[1–3]. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and long-term care[4]. The National Livelihood Survey also shows that cardiovascular disease (CVD) is ranked first in causing disabilities in the elderly[4]. Most CVD patients have multiple risk factors[5]. The presence of these risk factors in a specific combination, entitled metabolic syndrome (MS), is a multiplex risk factor that predisposes affected individuals to CVD morbidity and mortality. MS is generally considered a combination of being overweight (OW) and having hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT)[6].

Knee OA (KOA) and MS share age and obesity as risk factors[1,7–12]. Numerous investigators have associated OA with

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various MS components. Lawrence first reported that diastolic blood pressure (BP) was associated with KOA in women[13]. Kellgren reported that hand OA was significantly associated with above-average serum cholesterol levels in women[14]. Cimmino *et al.* observed significantly higher plasma glucose levels in women with OA than in those without[15]. Contradictory findings regarding the association of such metabolic factors with OA have been reported[16–19]. Hart *et al.* found that metabolic factors such as blood glucose, hypercholesterolaemia, and even treated HT were associated with KOA development[20]. A few population-based studies have demonstrated a dose–response relationship between risk factor accumulation for MS and KOA; we have previously reported that KOA presence was significantly associated with increase in the number of MS components[21]. However, to our knowledge, no study has clarified the associations between KOA occurrence or progression and MS component accumulation, using a prospective cohort of general inhabitants.

This study evaluated the incidence and progression of radiographic KOA and its associations with individual and cumulative MS components (OW, HT, DL, and IGT) among men and women using the large-scale, population-based cohort from the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

Method

Participants

This study involved the cohorts established in 2005 for the ROAD study. Details of the cohort profile have been reported elsewhere[22,23] and are only briefly described here. In 2005–2007, we created a baseline database including clinical information for 3,040 residents of Japan (men, 1,061; women, 1,979). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 individuals (men, 465; women, 885) from an urban region in Itabashi, Tokyo; 864 individuals (men, 319; women, 545) from a mountainous region in Hidakagawa, Wakayama; and 826 individuals (men, 277; women, 549) from a coastal region in Taiji, Wakayama. In 2008–2010, we attempted to locate and follow-up all 3,040 subjects. They were invited for the second survey of the ROAD study, a 3-year follow-up examination identical to the baseline examinations.

For the current study, we enrolled all 1,690 subjects (men, 596; women, 1,094) resided in the mountainous and coastal areas, where blood examination had been performed on all participants at baseline. All participants provided written informed consent, and the study was conducted with approval from the ethics committees of the University of Tokyo.

Baseline examination procedures

At the baseline examination, participants completed an interviewer-administered questionnaire of 400 items, including lifestyle information such as primary occupation; smoking habits (0: ex- or non-smoker, 1: current smoker); alcohol consumption (0: ex- or non-drinker, 1: current drinker); physical activity, including bicycling every day over the past 12 months (0: no, 1: yes); regular exercise (0: no, 1: yes); and medical history, including history of knee injuries (0: no, 1: yes). The participants were asked whether they took prescription medication daily or nearly every day (0: no, 1: yes). If they did not know what their medications were prescribed for, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height, weight, and body mass index [BMI: weight (kg)/height^2 (m^2)]. Systolic and diastolic BP was measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information, including information on knee joints, was collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot-map positioning.

All blood samples were obtained between 09:00 and 15:00. Haemoglobin A1c (HbA1c), blood sugar, high-density lipoprotein cholesterol (HDL-cho), total cholesterol, and triglyceride (TG) levels were measured. All analyses were performed at the same laboratory within 24 h of extraction (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

In this study, definitions of MS components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[24] and the Japan Society for the Study of Obesity[25]. However, because not all blood samples were obtained under fasting conditions, we used indices from the National Health and Nutrition Survey in Japan adopted as MS criteria in this national screening study due to the difficulty of collecting samples under fasting conditions[26]. The following definitions were used for MS components: OW, BMI $\geq$ 25 kg/m^2; HT, systolic BP $\geq$ 130 mm Hg and/or diastolic BP $\geq$ 85 mm Hg; DL, serum HDL-cho level $<$ 40 mg/dL; and IGT, serum HbA1c level $\geq$ 5.5%. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

Three-year follow-up and definition of KOA occurrence and progression

In 2008–2010, the 1,690 subjects were invited to attend the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those at baseline. Knee radiographs were read by a single experienced orthopaedist (SM) without knowledge of participants' clinical status and were categorized using the Kellgren–Lawrence (KL) grading scale[27]. When there were differences in the KL grades between the two knees, the higher KL grade was assigned to the participant. A subject with KL $\geq$ 2 was defined as having radiographic KOA. A new KOA case was identified if both knees had a KL grade $<$ 2 at baseline and if at least one knee developed a KL of $\geq$2 during follow-up. KOA progression was defined as the KL grade for either knee being higher during follow-up than at baseline.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the chi-square test. Differences in continuous variables were tested for significance using analysis of variance for multiple groups or Scheffe's least significant difference test for pairs of groups. All P values and 95% confidence intervals (CI) are two-sided.

To clarify associations between KOA occurrence or progression and MS risk factors, we performed three types of multivariate logistic regression analysis. Model 1 was performed using KOA occurrence or progression (over 3 years, 1: yes, 0: no) as the objective variable. Each risk factor for MS, that is, continuous variables such as BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels, and categorical variables such as OW (1: presence, 0: absence), HT (1: presence, 0: absence), DL (1: presence, 0: absence), and IGT (1: presence, 0: absence) were considered as an individual explanatory variable after adjusting for age and gender. Model 2 was performed using the same objective variable and individual explanatory factor for MS as in Model 1, after adjustment for age, gender, regional differences, smoking, alcohol

consumption, bicycling, regular exercise, and history of knee injuries, all of which had been found to be significantly associated with KOA presence in a previous study using the same population[17]. Model 3 was obtained by multivariate logistic regression analysis using the same objective variable and the same adjustment factors as in Model 2; furthermore, other MS components were included in the mutual adjustment model. For example, when BMI was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, systolic BP, and serum HDL-cho and HBA1c levels. Similarly, when OW was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, HT, DL, and IGT. Because systolic and diastolic BP was moderately correlated ($r = 0.5643$, $P < 0.001$), only values of systolic BP were used as representative of BP in Model 3.

To further evaluate associations between the number of MS components and KOA occurrence and progression, we used two multivariate logistic regression models. In Model 4, we used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, after adjusting for age and gender. In Model 5, we used KOA occurrence or progression as the objective variable and the number of MS components present as the explanatory variable, after adjusting for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, and history of knee injuries.

Results

Eligible participants

Of the 1,690 baseline survey participants, 251 (14.9%; men, 104; women, 147) dropped out of the follow-up study. The reasons for the drop-outs are shown in Fig. 1. In this study, we used the data for the remaining 1,384 subjects (81.9%; men, 466; women, 918) who completed all examinations in both baseline and follow-up surveys.

Table I shows baseline characteristics of the 1,384 participants and mean values for BMI, systolic and diastolic BP, and serum HDL-cho and HbA1c levels, classified by gender. Men had significantly higher BMI, higher systolic and diastolic BP, and lower serum HDL-cho levels than women. However, serum HbA1c levels did not show

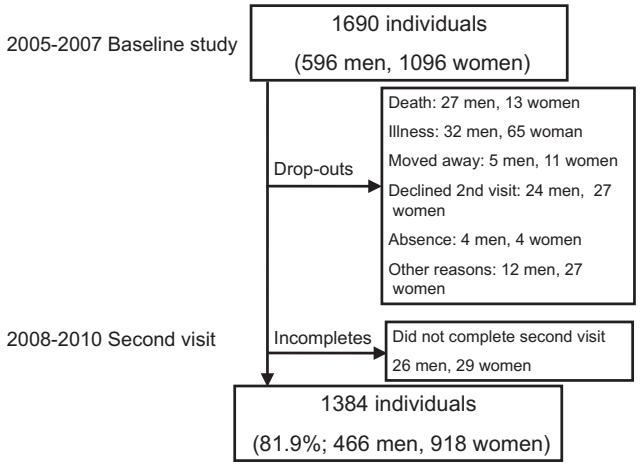


Fig. 1. Flow of participants in the baseline and second surveys.

Table I
Baseline characteristics of subjects who participated in both the first and second surveys

	Total	Men	Women	*P* (men vs women)
Number of subjects classified by age-strata (%)				
≤39 (year)	39 (2.8)	10 (2.1)	29 (3.2)	0.23
40–49	135 (9.8)	40 (8.6)	95 (10.3)	
50–59	298 (21.5)	99 (21.2)	199 (21.7)	
60–69	413 (29.8)	131 (28.1)	282 (30.7)	
70–79	404 (29.2)	155 (33.3)	249 (27.1)	
≥80	95 (6.9)	31 (6.7)	64 (7.0)	
Total	1384 (100.0)	466 (100.0)	918 (100.0)	
Means (standard deviations) of selected characteristics				
Age (year)	63.9 (11.8)	64.9 (11.6)	63.4 (11.9)	0.0246*
Height (cm)	155.6 (9.0)	164.0 (7.0)	151.3 (6.7)	<0.001***
Weight (kg)	56.0 (10.7)	62.1 (10.7)	52.5 (8.7)	<0.001***
Prevalence of selected characteristics, %				
Residing in a coastal area	54.1	51.9	55.2	0.245
Current smoking habit (more than once a month)	12.3	29.4	3.5	<0.001***
Current alcohol consumption (more than once a month)	40.6	68.2	26.6	<0.001***
Bicycling every day in the past 12 months	55.5	55.2	55.7	0.859
Regular exercise, i.e., football, tennis, baseball, or golf, after graduation from school (%)	15.3	36.1	4.7	<0.001***
Past injury of either knee (%)	2.5	1.9	2.8	0.313
Medication for components of MS, %				
Medication for HT	29.8	27.5	31.1	0.169
Medication for DL	7.2	3.4	9.2	<0.001***
Medication for diabetes mellitus, including insulin injection	5.6	7.3	4.8	0.056
Mean values (standard deviations) for components of MS				
BMI (kg/m^2)	23.1 (3.4)	23.4 (3.2)	22.9 (3.4)	0.0089
Systolic BP (mm Hg)	134.1 (20.4)	136.6 (18.3)	132.9 (21.4)	0.0015**
Diastolic BP (mm Hg)	74.2 (11.4)	77.0 (11.5)	72.8 (11.0)	<0.0001***
Serum levels of HDL-cho (mg/dL)	61.2 (15.9)	55.8 (16.1)	64.0 (15.0)	<0.0001***
Serum levels of HbA1c (%)	5.19 (0.73)	5.23 (0.85)	5.17 (0.67)	0.1900
Prevalence of components of MS, %				
OW	25.7	28.1	24.4	0.135
HT	67.2	72.7	64.4	0.002**
DL	13.0	15.2	11.9	0.079
IGT	21.1	24.7	19.3	0.020*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

significant gender-based differences. In the total population, the MS component with the highest prevalence was HT, followed by OW, IGT, and DL. The prevalences of HT and IGT were significantly higher in men than in women.

KOA occurrence and progression and MS components

Baseline KOA prevalence in the 1,384 individuals was 46.8% (men, 37.3%; women, 51.6%). After exclusion of subjects having KOA (KL grade ≥ 2 in at least one knee) at baseline, the cumulative KOA incidence during the 3-year follow-up was estimated using a population-at-risk of 728 individuals (men, 290; women, 438) without

KOA in either knee at baseline. Among these subjects, 71 new KOA cases (men, 18; women, 53) were detected, with a cumulative incidence of 3.3%/year (men, 2.1%/year; women, 4.0%/year). After excluding subjects with KL grade = 4 for at least one knee at baseline, the progression rate over the 3-year follow-up was estimated using the population-at-risk of 1,296 individuals (men, 445; women, 851). Among these, 311 individuals (men, 86; women, 225) had a higher KL grade for one or both knees at follow-up than at baseline. The progression proportion of the KL grade for either knee over the 3-year period was 24.0% (8.0%/year; men, 6.4%/year; women, 8.8%/year) in the overall population-at-risk.

Table II shows cumulative KOA incidence and progression, classified by age groups of ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, which significantly increased with age. BMI, systolic BP, and HbA1c levels at baseline were significantly higher and HDL-cho levels significantly lower in subjects with KOA than in those without KOA. Similar to KOA, BMI, systolic BP, and HbA1c levels were significantly higher and HDL-cho levels significantly lower in subjects with KL grade progression than in those without. This tendency was much more pronounced in women than in men.

Table III shows multivariate logistic regression analysis results for KOA occurrence vs values for each MS component, including BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels measured at baseline (Table III). Model 2 showed that BMI, systolic BP, and serum HDL-cho levels were significantly associated with KOA occurrence after adjustment for various risk factors. However, Model 3, incorporating mutual adjustment for each MS component, indicated that only BMI was significantly associated with KOA occurrence. The three types of multivariate logistic regression analyses using KOA progression as the objective factor showed similar results as for KOA occurrence described above.

Table IV shows associations between KOA occurrence and MS risk factors. Both Models 1 and 2 revealed that OW, HT, and IGT were significantly associated with KOA. Analysis using OW, HT, DL, and IGT as explanatory variables with mutual adjustment (Model 3) indicated that HT and IGT were significantly associated with KOA. Table IV also shows associations between KOA progression and MS risk factors, indicating that OW and HT were significantly associated with KOA progression. Although IGT was significantly associated with KOA progression after adjustment for age and gender, the effect diminished after adjustment for various other risk factors.

KOA occurrence and progression and the number of MS components

Figure 2 shows the cumulative KOA incidence (%/year) classified by the number of MS components present. In the total population, the cumulative incidence classified by the number of MS

Table II
Mean values (standard deviations) for components of MS vs occurrence and progression of KOA

	Total			Men			Women		
	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*
	(*n* = 657)	(*n* = 71)		(*n* = 272)	(*n* = 18)		(*n* = 385)	(*n* = 53)	
Occurrence of KOA									
Number of subjects classified by age-strata (cumulative incidence, %/year)									
≤39 (year)	38	0 (0.0)	<0.001	10	0 (0.0)	0.009	28	0 (0.0)	<0.001
40–49	118	1 (0.3)		36	0 (0.0)		82	1 (0.4)	
50–59	201	15 (2.3)		77	0 (0.0)		124	15 (3.6)	
60–69	177	27 (4.4)		76	11 (4.2)		101	16 (4.6)	
70–79	108	23 (5.9)		62	6 (2.9)		46	17 (9.0)	
≥80	15	5 (8.3)		11	1 (2.8)		4	4 (16.7)	
Mean values (standard deviations) for age and components of MS									
Age (year)	58.2 (11.8)	67.3 (8.2)	<0.0001	61.0 (11.8)	70.0 (6.1)	0.0021	56.4 (11.4)	66.4 (8.7)	<0.0001
BMI (kg/m^2)	22.4 (3.2)	23.6 (2.9)	0.0035	23.2 (3.2)	24.2 (3.1)	0.1709	21.9 (3.1)	23.4 (2.8)	0.0012
Systolic BP (mm Hg)	129.6 (19.4)	138.2 (19.1)	0.0005	133.4 (17.9)	143.4 (17.7)	0.0255	127.0 (20.0)	136.5 (19.4)	0.0014
Diastolic BP (mm Hg)	74.3 (11.2)	74 (11.0)	0.8599	77.5 (11.8)	76.7 (10.7)	0.7907	72.0 (10.2)	73.2 (11.0)	0.4544
Serum levels of HDL-cho (mg/dL)	63.4 (16.8)	59.2 (13.3)	0.0414	57.3 (16.3)	54.6 (15.7)	0.5017	67.7 (15.8)	60.8 (12.1)	0.0021
Serum levels of HbA1c (%)	5.11 (0.67)	5.32 (0.79)	0.0142	5.24 (0.87)	5.09 (0.75)	0.4644	5.01 (0.46)	5.39 (0.80)	<0.0001
	Total			Men			Women		
	Progression (−) (*n* = 985)	Progression (+) (*n* = 311)	*P*	Progression (−) (*n* = 359)	Progression (+) (*n* = 86)	*P*	Progression (−) (*n* = 626)	Progression (+) (*n* = 255)	*P*
Progression of KOA									
Number of subjects classified by age-strata (proportion of progression, %/year)									
≤39 (year)	37	2 (1.7)	<0.001***	9	1 (3.3)	<0.001***	28	1 (1.1)	<0.001***
40–49	128	7 (1.7)		38	2 (1.7)		90	5 (1.8)	
50–59	248	44 (5.0)		89	8 (2.8)		159	36 (6.2)	
60–69	292	105 (8.2)		101	26 (6.8)		191	79 (9.8)	
70–79	241	115 (10.8)		105	38 (8.9)		136	77 (12.1)	
≥80	39	38 (16.5)		17	11 (13.1)		22	27 (18.4)	
Mean values (standard deviations) for age and components of MS									
Age (year)	61.6 (11.9)	68.7 (9.3)	<0.0001***	63.3 (11.8)	70.0 (9.4)	<0.0001***	60.7 (11.9)	68.2 (9.3)	<0.0001***
BMI (kg/m^2)	22.7 (3.3)	23.6 (3.1)	<0.0001***	23.2 (3.2)	23.9 (3.1)	0.0643	22.4 (3.3)	23.5 (3.1)	<0.0001***
Systolic BP (mm Hg)	132.2 (20.0)	137.9 (19.3)	<0.0001***	135.4 (17.9)	138.6 (17.0)	0.1390	130.4 (20.9)	137.6 (20.1)	<0.0001***
Diastolic BP (mm Hg)	74.0 (11.2)	74.5 (11.8)	0.5517	77.1 (11.6)	76.3 (10.6)	0.5698	72.3 (10.5)	73.8 (12.2)	0.0792
Serum levels of HDL-cho (mg/dL)	62.3 (16.6)	59.0 (13.8)	0.0018**	56.7 (16.4)	53.5 (15.2)	0.0921	65.4 (15.8)	61.1 (12.6)	0.0003***
Serum levels of HbA1c (%)	5.15 (0.72)	5.27 (0.74)	0.0133*	5.20 (0.84)	5.30 (0.88)	0.3687	5.11 (0.64)	5.25 (0.68)	0.0069**

KOA(−), non-occurrence of KOA; KOA(+), occurrence of KOA; progression(−), no progression of the KL grade; progression(+), progression of the KL grade.
n, number of subjects.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table III
ORs for occurrence and progression of KOA during the 3-year follow-up period vs BMI, systolic and diastolic BP, serum levels of HDL-cho, and HbA1c level

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	*P*	Adjusted OR2	95% CI	*P*	Adjusted OR3	95% CI	*P*
Occurrence of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.22	1.12–1.33	<0.001***	1.22	1.12–1.34	<0.001***	1.18	1.07–1.30	0.001**
Systolic BP (mm Hg)	+1 mm Hg	1.54	0.87–2.72	0.136	1.01	1.00–1.03	0.038*	1.01	1.00–1.03	0.188
Diastolic BP (mm Hg)	+1 mm Hg	1.51	0.71–3.19	0.282	1.01	0.99–1.04	0.373	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.980	0.962–0.999	0.039*	0.980	0.960–0.999	0.039*	0.989	0.968–1.009	0.256
Serum levels of HbA1c (%)	+1%	1.29	0.92–1.81	0.136	1.34	0.96–1.88	0.089	1.07	0.73–1.56	0.743
Progression of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.12	1.08–1.17	<0.001***	1.13	1.08–1.18	<0.001***	1.11	1.06–1.17	<0.001***
Systolic BP (mm Hg)	+1 mm Hg	1.47	1.10–1.97	0.010*	1.01	1.00–1.01	0.039*	1.00	1.00–1.01	0.352
Diastolic BP (mm Hg)	+1 mm Hg	1.33	0.92–1.91	0.124	1.01	1.00–1.025	0.057	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.988	0.979–0.997	0.011*	0.987	0.978–0.997	0.008**	0.992	0.983–1.002	0.137
Serum levels of HbA1c (%)	+1 %	1.11	0.94–1.33	0.227	1.11	0.93–1.32	0.277	0.99	0.81–1.19	0.881

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes), and other potential risk factors such as BMI, systolic BP, serum levels of HDL-cho, and HbA1c levels, mutually.

components (0, 1, 2, or ≥3) was 1.0, 3.5, 3.4, and 8.7, respectively, which increased with the number of MS components (*P* for trend < 0.001). Figure 2(A) also shows the cumulative KOA incidence according to the number of MS components by gender. The cumulative incidence among individuals with one or more MS components was higher in women than in men.

Figure 2 also shows KL grade progression (%/year) for either knee classified by the number of MS components present. In the total population, KL grade progression classified by 0, 1, 2, or ≥3 MS components was 4.3, 7.6, 10.8, and 11.3, respectively, which significantly increased with the number of MS components (*P* for trend < 0.001). The progression among individuals with one or more MS components was higher in women than in men [Fig. 2(B)].

To further illustrate the effects of the number of MS components on KOA occurrence and progression, Fig. 3 presents the results of the multivariate logistic regression analysis models for KOA occurrence. Model 4 used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, adjusted

Table IV
ORs for occurrence and progression of KOA during the 3-year follow-up period vs risk factors for MS

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	*P*	Adjusted OR2	95% CI	*P*	Adjusted OR3	95% CI	*P*
Occurrence of KOA										
Component of MS										
OW	Yes vs no	2.36	1.28–4.34	0.006**	2.46	1.32–4.59	0.005**	1.71	0.88–3.33	0.114
HT	Yes vs no	3.02	1.47–6.23	0.003**	3.27	1.57–6.80	0.002**	2.74	1.30–5.78	0.008**
DL	Yes vs no	1.34	0.65–2.73	0.425	1.55	0.75–3.23	0.240	1.20	0.55–2.59	0.646
IGT	Yes vs no	2.42	1.37–4.27	0.002**	2.47	1.38–4.41	0.002**	1.94	1.05–3.59	0.033*
Progression of KOA										
Component of MS										
OW	Yes vs no	1.76	1.30–2.38	<0.001***	1.87	1.37–2.55	<0.001***	1.66	1.21–2.29	0.002**
HT	Yes vs no	1.75	1.26–2.42	0.001**	1.75	1.26–2.43	0.001**	1.54	1.10–2.17	0.012*
DL	Yes vs no	1.18	0.81–1.71	0.400	1.36	0.93–2.01	0.117	1.26	0.85–1.87	0.248
IGT	Yes vs no	1.42	1.04–1.94	0.029*	1.35	0.98–1.87	0.068	1.18	0.84–1.64	0.336

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Being OW was defined as BMI ≥ 25 kg/m^2, HT as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum HDL-cho level < 40 mg/dL, and IGT as serum HbA1c level ≥ 5.5%. Further, subjects being treated with medication for HT, DL, or IGT were regarded as having the respective disorder.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, or IGT) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, and IGT) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and being OW, HT, DL, and IGT as explanatory variables, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), past history of knee injuries (0: no, 1: yes), and other components of MS, mutually.

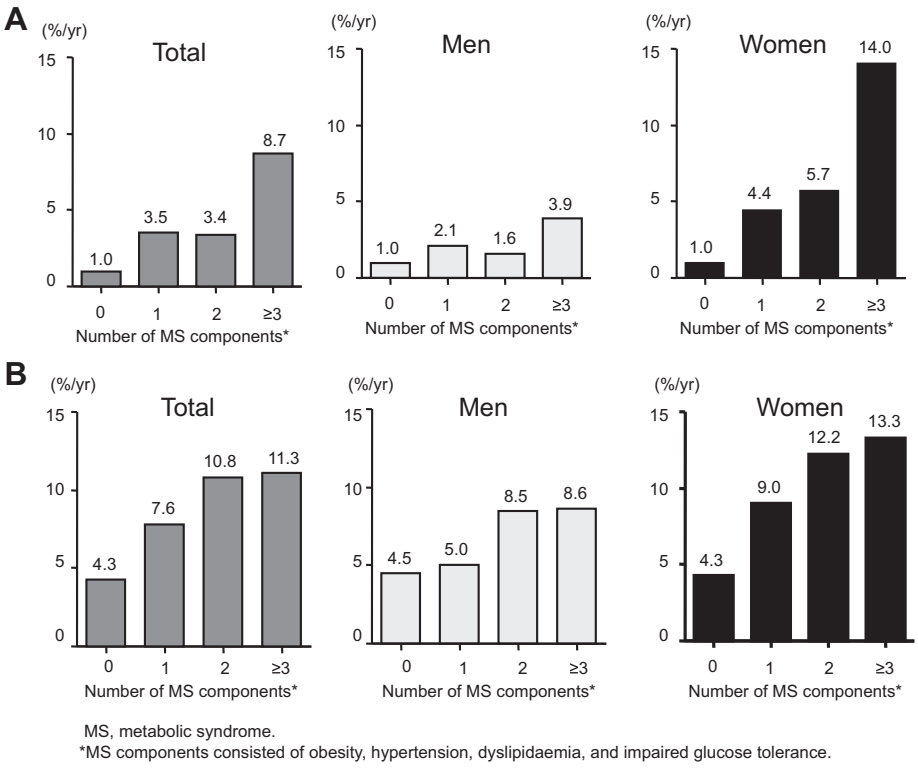
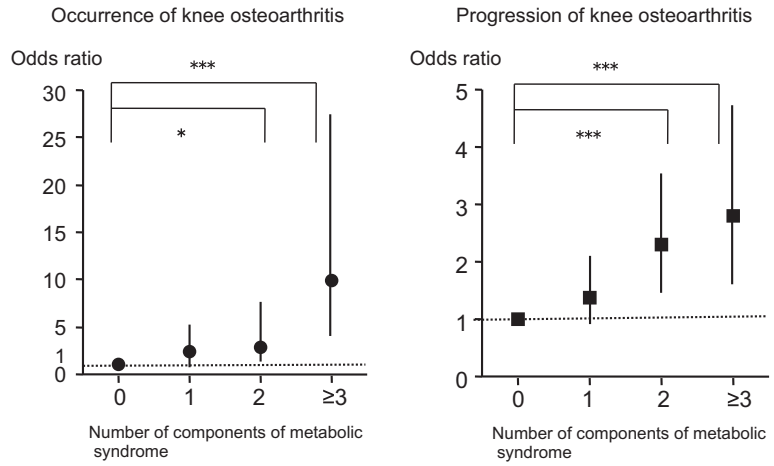


Fig. 2. Cumulative incidence (%/year) of KOA (A) and progression of the KL grade of either knee (%/year) (B) classified by the number of components of MS, including OW, HT, DL, and IGT.

for age and gender. The odds ratio (OR) and 95% CI for KOA occurrence were found to significantly increase with the number of MS components present (OR, 95% CI vs no component: one component, 2.16, 0.90–5.20, $P = 0.085$; two components, 2.49, 0.95–6.55, $P = 0.063$; ≥three components, 8.38, 3.12–22.5, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present (OR, 95% CI vs no component: one component, 1.41, 0.94–2.12, $P = 0.097$; two components, 2.25, 1.47–3.46, $P < 0.001$; ≥three components: 2.59, 1.57–4.27, $P < 0.001$).

Logistic regression model results obtained using KOA occurrence or progression as the objective variable and the number of MS components present as explanatory variables, after adjusting for age, gender, and the other potential risk factors listed in the Methods section, are shown in Fig. 3. The OR significantly increased with the number of MS components present after adjustment for



*:p < 0.05,***:p < 0.001

Multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and the number of MS components as the explanatory variable, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: curre nt drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

Fig. 3. ORs for occurrence and progression of KOA during the 3-year follow-up period vs the number of risk factors for MS.

other risk factors (OR, 95% CI vs no component: one component, 2.33, 0.96–5.65, $P = 0.065$; two components, 2.82, 1.05–7.54, $P = 0.039$; ≥three components, 9.83, 3.57–27.1, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present after adjustment for other risk factors (OR, 95% CI vs no component: one component, 1.38, 0.91–2.08, $P = 0.126$; two components, 2.29, 1.49–3.54, $P < 0.001$; ≥three components: 2.80, 1.68–4.68, $P < 0.001$). In both models, the OR for KOA occurrence significantly increased with the number of MS components present. Similar trends were observed for KOA progression with both models.

Discussion

In this study, we determined the cumulative incidence and progression rate of KOA diagnosed using the KL scale. We demonstrated that KOA occurrence and progression are associated with higher systolic BP, lower serum HDL-cho levels, and higher serum HbA1c levels, as well as higher BMI. Incorporating mutual adjustment for each MS component indicated that only BMI was significantly associated with KOA occurrence and progression. Regarding the risk factors for MS and KOA, even after adjusting for potential risk factors, multivariate analysis determined that HT and IGT were significantly associated with KOA occurrence, and OW and HT were significantly associated with KOA progression. The presence of a greater number of MS components was associated with a higher rate of KOA occurrence and progression. This tendency was much more pronounced in occurrence of KOA than in progression.

Numerous reports have presented an association between being OW or obese and KOA[1,7–12]. Lohmander *et al.* reported that being OW was associated with higher KOA incidence, and among measures of excess weight, BMI was observed to have the strongest relative risk gradient[28]. In the present study, we confirmed that BMI was the only continuous value significantly associated with KOA occurrence and progression among the MS risk factors (e.g., BMI, systolic BP, and serum levels of HDL-cho and HbA1c), consistent with previous studies. In contrast, several reports have shown that HT is associated with KOA presence, independent of OW[20,29–31]. In the present study, we confirmed a significant association between HT and IGT and KOA occurrence, and between OW and HT and KOA progression. Although several studies have found that obesity or increased BMI were risk factors for KOA onset[32–35], this appears to be the first report of associations between MS risk factors other than OW and KOA occurrence and progression.

There were differences between the results for continuous variables such as BMI, BP, and serum HDL-cho and HbA1c levels and those for categorical clinical criteria such as OW, HT, DL, and IGT. In analysis involving continuous variables, BMI was the only predictor of future KOA occurrence or progression. In contrast, clinical criteria-based analysis clearly showed associations between metabolic risk factors other than OW and KOA. This discrepancy suggests that the clinical criterion for OW (BMI ≥ 25 kg/m^2) may be less sensitive than continuous BMI values in reflecting the association of excess weight with KOA. We then performed additional analyses using KOA occurrence or progression as the objective variable and categorical risk factors for MS, such as HT, DL, and IGT, as explanatory variables. We also added continuous values for BMI at baseline rather than OW, after adjusting for multiple risk factors as listed for Model 2. The resulting overall ORs for HT, DL, and IGT adjusted for BMI on KOA occurrence or progression became smaller than those adjusted for OW. However, the association between HT and KOA occurrence remained significant (OR, 2.43; 95% CI, 1.14–5.18; $P = 0.021$), while IGT was no longer significant (OR, 1.70; 95% CI, 0.91–3.19; $P = 0.096$). Similarly, the association between HT and KOA progression remained significant (OR, 1.41; 95% CI, 1.00–2.00; $P = 0.049$). These results indicate that, even if associations between KOA and categorical MS components other than BMI are weak, if adjustments are made for OW using clinical criteria, then HT and IGT may be risk factors for KOA occurrence and HT may be a risk factor for KOA progression.

Regarding ethnic differences in KOA, we previously reported that KOA prevalence and incidence in the original ROAD study of 3,040 baseline participants was higher than those of Caucasians[36,37]. In contrast, with regard to ethnic differences in MS, Hoang *et al.* reviewed epidemiological studies and reported that MS prevalence in East Asians was lower than that in Caucasians[38]. MS prevalence in Asia may be increasing rapidly, as Nestel *et al.* reported a substantial increase in a cohort from Beijing from 9% in 1992 to 21% in 2002[39]. These ethnic differences have been suggested as resulting from genetic factors that modulate the association between KOA and obesity[40,41].

Regarding associations between risk factors of MS and KOA, Hart *et al.* attributed the effect of excess endogenous oestrogens to aromatization of oestrone in fat tissue[20]. Sowers *et al.* suggested that leptin and adiponectin levels influenced OA development[29]. Another hypothesis suggests that in obese subjects, metabolic changes in the striated muscles induced by interactions between insulin resistance and systemic inflammation may lead to fatigue and muscle weakness, influencing the balance between damage and repair mechanisms and ultimately leading to OA[42,43]. Inflammatory factors are suggested to be associated with both obesity and KOA[44,45]. Findlay evaluated the concept that vascular pathology might play a role in the initiation and/or progression of OA[46] and proposed that peripheral reduced blood flow associated with HT caused subchondral ischaemia. This ischaemia may in turn compromise nutrient and gas exchange into the articular cartilage and contribute to apoptosis of regional osteocytes of the subchondral bone. Furthermore, chondrocytes of OA exposed to high glucose concentrations exhibit impaired glucose transporter-1 downregulation[47]. Thus, impaired glucose transporter-1 downregulation may constitute an important pathogenic mechanism by which conditions characterized by hyperglycaemia may promote degenerative changes in chondrocytes, facilitating OA progression. However, in the present study, after adjustment for BMI, the effect of IGT was weak. Further studies are required to confirm whether IGT is a risk factor for KOA occurrence. Furthermore, because the present study aimed to identify associations between metabolic risk factors and future KOA occurrence or progression, we did not evaluate the effects of genetic factors and other risk factors potentially influencing MS and KOA. However, additional risk factors for both conditions should be addressed in further analysis of the ROAD study.

No previous studies have been performed on metabolic risk factor clustering and KOA occurrence or progression, although some cross-sectional epidemiological studies have evaluated the association between metabolic risk factor clustering and KOA presence[29,31]. In the present study, we demonstrated that KOA occurrence and progression are influenced not only by individual MS components but also by their clustering. An increase in the number of MS components significantly increases the risk of both KOA occurrence and progression. This effect of clustering was stronger for KOA occurrence than for KOA progression. Combining the present results with those of our previous report using the same analytical methods and adjustment factors[21], the ORs for ≥three components vs no components were 9.95, 2.79, and 2.72 for KOA occurrence, progression, and presence, respectively. Thus, preventing MS would aid in reducing every stage of KOA, including onset, worsening, and presence.

This study has several limitations. First, although it includes a relatively large number of participants, these participants do not

represent the entire general population because they were recruited from only two areas. Regarding potential selection bias of the ROAD study, we previously reported that no significant differences were identified between our participants and the general Japanese population, except that male participants aged 70–74 years in the ROAD study were significantly smaller in terms of body structure than the overall Japanese population ($P < 0.05$)[23]. Although we could locate and include baseline participants after 3 years with a high participation rate, this selection bias at baseline should be considered when generalising the results. Second, the definitions used for MS components were not completely identical to international criteria such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, World Health Organization (WHO), or The American Association of Clinical Endocrinologists (AACE)[48]. As there has been considerable debate regarding abdominal circumference ($\geq$85 cm in men, $\geq$90 cm in women) in the Japanese criteria[49], we decided to utilize BMI $\geq$ 25 kg/m^2 to indicate OW rather than abdominal circumference. Furthermore, because not all blood samples were obtained under fasting conditions, we did not use blood glucose and serum TG levels as indicators. Therefore, our results may underestimate the presence of MS components, especially DL and IGT. However, we used the alternative index for each condition, recommended by the National Health and Nutrition Survey for cases where collecting samples under fasting conditions is difficult[26], and thus our criteria likely reflect dysfunction in lipid and glucose metabolism. Finally, we used KL grade $\geq$ 2 for diagnosing KOA. However, the KL scale is a categorical index, and it is impossible to evaluate the minimum joint space and osteophytosis separately. To evaluate KOA severity using quantitative parameters, a KOA computer-assisted diagnostic system[50] measuring minimum joint space width and osteophytosis area is under development; this system will provide increased accuracy in determining the association between MS components and KOA development for early prevention of disability.

In conclusion, this study revealed that HT and IGT influence KOA occurrence and that OW and HT are associated with KOA progression. KOA occurred or worsened more frequently with increase in the number of MS components. Preventing MS may be useful in preventing both KOA occurrence and progression.

Author contributions

NY conceptualized the study, was primarily responsible for developing the protocol, and acts as the guarantor for this study. SM, HO, and TA conducted data collection and X-ray assessment. All authors reviewed the protocol and contributed to interpretation of the results. All authors were involved in drafting the article and approved the final version submitted for publication. All authors had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analyses.

Role of the funding source

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Conflict of interest

All authors declare that (1) no authors have received corporate support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) the authors' spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

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